**ModernaTX, Inc.**

**mRNA-1345-P304**

# A Phase 3, Randomized, Observer-blind Study to Evaluate Safety, Tolerability, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, When Coadministered With a High-dose, Quadrivalent Seasonal Influenza Vaccine in Adults ≥65 Years of Age

**Statistical Analysis Plan**
**Version 1.0**
**Date Issued: 10-Nov-2023**

Prepared by:

PPD, part of Thermo Fisher Scientific
929 North Front Street
Wilmington, NC 28401

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# DOCUMENT HISTORY

| Version | Date | Description of major modifications |
|---|---|---|
| 1.0 | 10-Nov-2023 | Final Version |

## List of Abbreviations

| Abbreviation | Definition |
|---|---|
| Ab | Antibody |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ANCOVA | Analysis of covariance |
| AR | Adverse reaction |
| ATC | Anatomical Therapeutic Chemical |
| bAb | Binding antibody |
| BMI | Body mass index |
| CDC | Center for Disease Control and Prevention |
| CEAC | Cardiac Event Adjudication Committee |
| CI | Confidence interval |
| CRF | Case report form |
| CRO | Contract research organization |
| CSP | Clinical study protocol |
| CSR | Clinical study report |
| DBL | Database lock |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| eDiary | Electronic diary |
| EoS | End of study |
| FAS | Full analysis set |
| GLSM | Geometric least squares mean |
| GMFR | Geometric mean fold-rise |
| GM | Geometric mean |
| GMC | Geometric mean concentration |
| GMR | Geometric mean titer ratio |
| GMT | Geometric mean titer |
| HA | Hemagglutination |
| HAI | Hemagglutination inhibition |
| HCP | Healthcare practitioner |
| HD | High-dose |
| HLGT | High level group term |
| IA | Interim analysis |
| IcEv | Intercurrent event |
| IM | Intramuscular(ly) |
| IP | Investigational product |
| IRT | Interactive Response Technology |
| LB | Lower bound |
| LLOQ | Lower limit of quantification |
| MAAE | Medically-attended adverse event |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |

| Abbreviation | Definition |
|---|---|
| PP | Per-protocol |
| PT | Preferred term |
| RSV | Respiratory Syncytial Virus |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SAS | Statistical analysis system |
| SCR | Seroconversion rate |
| SD | Standard deviation |
| SOC | System organ class |
| SMQ | Standardized MedDRA Queries |
| SRR | Seroresponse rate |
| TFLs | Tables, Figures, and Listings |
| ULOQ | Upper limit of quantification |
| WHO-DD | World Health Organization Drug Dictionary |

# 1. Introduction

This statistical analysis plan (SAP), version 1.0, is based on the approved clinical study protocol (CSP) (original version, dated 21-Jul-2023) and the approved eCRF (version 1.0, dated on 20-Sep-2023).

In addition to the information presented in the statistical consideration sections of the protocol (Section 9) which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan which are not "principal" in nature and result from information that was not available at the time of protocol finalization. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

Study mRNA-1345-P304 is a Phase 3, randomized, observer-blind study to evaluate safety, tolerability, and immunogenicity of mRNA-1345, an mRNA vaccine targeting respiratory syncytial virus (RSV), when coadministered with a high-dose (HD), quadrivalent seasonal influenza vaccine in adults ≥65 years of age.

PPD Biostatistics and programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis. Statistical Analysis System (SAS) Version 9.4 or higher will be used.

In this document, intervention, injection and dose are used interchangeably.

# 2. Study Objectives

## 2.1. Primary Objectives

### 2.1.1. Primary Safety Objective

The primary safety objective of the study is to evaluate the safety and reactogenicity of mRNA-1345 RSV vaccine coadministered with a HD quadrivalent seasonal influenza vaccine (Fluzone HD).

### 2.1.2. Primary Immunogenicity Objectives

The primary immunogenicity objectives are:

- To evaluate the impact of coadministered HD quadrivalent seasonal influenza vaccine on the immune response to mRNA-1345 RSV vaccine against RSV-A and RSV-B.
- To evaluate the impact of coadministered mRNA-1345 RSV vaccine on the immune response to HD quadrivalent seasonal influenza vaccine against 4 vaccine-matched influenza A and B strains.

### 2.2. Secondary Objectives

The secondary immunogenicity objectives are:

- To further evaluate the effect of mRNA-1345 RSV vaccine coadministered with a HD quadrivalent seasonal influenza vaccine on the immune response to RSV-A and RSV-B.
- To further evaluate the effect of mRNA-1345 RSV vaccine coadministered with a HD quadrivalent seasonal influenza vaccine on the immune response against 4 vaccine-matched influenza A and B strains.

### 2.3. Exploratory Objectives

The exploratory objectives, which may be performed, are as follows:

- To further characterize the immune response across study vaccines

## 3. Study Endpoints

### 3.1. Primary Endpoints

#### 3.1.1. Primary Safety Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Solicited local and systemic ARs through 7 days after each injection.
- Unsolicited AEs through 21 days after each study injection.
- MAAEs from Day 1 to Month 6 after last study injection/EoS.
- AESI from Day 1 to Month 6 after last study injection/EoS.
- SAEs from Day 1 to Month 6 after last study injection/EoS.
- AEs leading to discontinuation from Day 1 to Month 6 after last study injection/EoS.

#### 3.1.2. Primary Immunogenicity Endpoints

The primary immunogenicity objectives will be evaluated by the following coprimary endpoints:

- Geometric mean titer (GMT) of serum RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2).

  **Note:** Arm 1 = Fluzone HD+mRNA-1345 CCI µg on Day 1 followed by placebo on Day 22 and Arm 2 = Fluzone HD+placebo on Day 1 followed by mRNA-1345 CCI µg on Day 22.

- GMT of serum influenza anti-HA Abs as measured by hemagglutination inhibition (HAI) assay at Day 22.

### 3.2. Secondary Endpoints

The secondary immunogenicity objectives will be evaluated by the following endpoints:

- Seroresponse rate (SRR) in RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2).
    - Seroresponse is defined as a postinjection titer ≥4 × LLOQ if baseline is <LLOQ or a ≥4-fold increase from baseline if baseline is ≥LLOQ.
- Geometric mean fold rise (GMFR) of postinjection RSV-A and RSV-B nAbs (Day 22 for Arm 1 and Day 43 for Arm 2) compared to baseline (Day 1 for Arm 1 and Day 22 for Arm 2).
- Proportion of participants with ≥2-fold increase in RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2).
- Seroconversion rate (SCR) in influenza anti-HA Abs as measured by HAI assay at Day 22.
    - Seroconversion is defined as a postinjection titer ≥1:40 if baseline is <1:10 or a ≥4-fold rise from baseline in postinjection titer if baseline is ≥1:10.
- GMFR of postinjection influenza anti-HA Abs at Day 22 compared to baseline ( Day 1) as measured by HAI assay.

### 3.3. Exploratory Endpoints

The exploratory objective will be evaluated by the following endpoints:

- Geometric mean concentration (GMC) and GMFR of postinjection/baseline titers of RSV bAbs.
- Proportions of participants with ≥2-fold and ≥4-fold increases in RSV bAb concentration postinjection.
- Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses.

## 4. Study Design

### 4.1. Overall Study Design

This is a Phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of mRNA-1345, an mRNA vaccine targeting RSV, given sequentially (3 weeks apart) or coadministered with a HD quadrivalent seasonal influenza vaccine (Fluzone HD) in adults ≥65 years of age.

All participants will participate in a Screening period (up to 28 days before Day 1), Intervention period (vaccine[s] and/or placebo administration on Day 1 and Day 22), and a Follow-up period (up to 7 months). The schematic of study arms and major study events is illustrated in Figure 1 and the schedule of activities (SoA) is provided in Appendix F.

The study will enroll approximately 1900 medically stable adults ≥65 years of age. On Day 1, each participant will receive 2 injections, one in each arm. On Day 22, each participant will receive 1 injection. All injections will be administered IM, in the deltoid muscle. Participants will be randomized to study arms as shown in Table 1 to receive either 1) Fluzone HD+mRNA-1345 CCI µg on Day 1 followed by placebo (0.9% sodium chloride) on Day 22 (Arm 1); or 2) Fluzone HD+placebo (0.9% sodium chloride) on Day 1 followed by mRNA-1345 CCI µg on Day 22 (Arm 2).

**Figure 1: Study Schema**

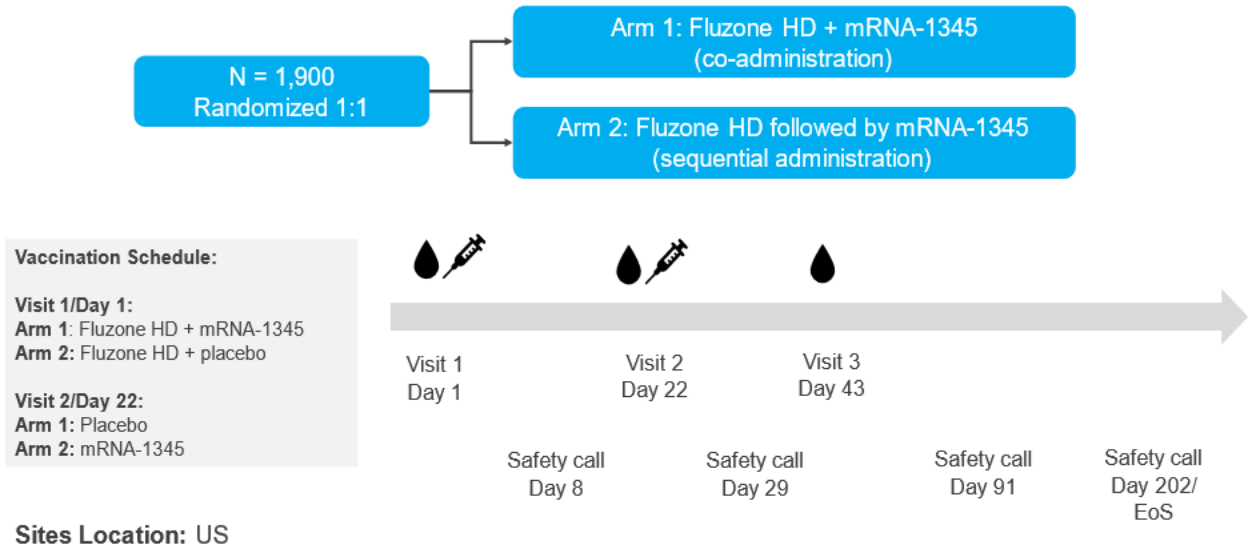


**Table 1: Randomized Groups**

| Arm Title | Arm 1 | Arm 2 |
|---|---|---|
| Arm Description | Day 1: Fluzone HD+mRNA-1345 CCI µg followed by<br>Day 22: Placebo | Day 1: Fluzone HD+Placebo followed by<br>Day 22: mRNA-1345 CCI µg |

## 4.2. Statistical Hypothesis

The immunogenicity primary objectives are to evaluate the effect of coadministered influenza vaccine with mRNA-1345 on the immune response to RSV-A and RSV-B virus and influenza A and B strains included in Fluzone HD. There are 6 coprimary endpoints to support the primary objectives.

**Primary Objective to Evaluate the Impact on the Immune Response to RSV-A:**

Coprimary endpoints based on RSV-A GMT 21 days after mRNA-1345 administration:

The null hypothesis $H_0^1$: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Fluzone HD, as measured by GMT at Day 22 (Arm 1) using RSV-A nAb assay, is inferior compared with that in participants who received mRNA-1345 sequentially with Fluzone HD, as measured by GMT at Day 43 (Arm 2) using RSV-A nAb assay. The noninferiority in the GMT in participants who received mRNA-1345 coadministered with Fluzone HD compared with that of participants who received mRNA-1345 sequentially with Fluzone HD will be demonstrated by the lower bound (LB) of the 95% CI of GMT ratio (GMR) of ruling out 0.667 (i.e., LB >0.667), using a noninferiority margin of 1.5. The GMR is the ratio of the GMT of RSV-A nAbs in participants who received mRNA-1345 coadministered with Fluzone HD compared with the GMT of RSV-A nAbs in participants who received mRNA-1345 sequentially with Fluzone HD.

**Primary Objective to Evaluate the Impact on the Immune Response to RSV-B:**

Coprimary endpoints based on RSV-B GMT 21 days after mRNA-1345 administration:

The null hypothesis $H_0^2$: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Fluzone HD, as measured by GMT at Day 22 (Arm 1) using RSV-B nAb assay, is inferior compared with that in participants who received mRNA-1345 sequentially with Fluzone HD, as measured by GMT at Day 43 (Arm 2) using RSV-B nAb assay. The noninferiority in the GMT in participants who received mRNA-1345 coadministered with Fluzone HD compared with that of participants who received mRNA-1345 sequentially with Fluzone HD will be demonstrated by the lower bound (LB) of the 95% CI of GMR of ruling out 0.667 (i.e., LB >0.667), using a noninferiority margin of 1.5. The GMR is the ratio of the GMT of RSV-B nAbs in participants who received mRNA-1345 coadministered with Fluzone HD compared with the GMT of RSV-B nAbs in participants who received mRNA-1345 sequentially with Fluzone HD.

**Primary Objective to Evaluate the Impact on the Immune Response to Influenza:**

Coprimary endpoints based on GMT 21 days after Fluzone HD administration:

The null hypotheses $H_0^3$ to $H_0^6$: immunogenicity response to Fluzone HD in participants who received mRNA-1345 coadministered with Fluzone HD, as measured by GMT of influenza anti-HA Abs for each of the 4 influenza strains at Day 22 (both Arm 1 and Arm 2) using HAI assay, is inferior compared with that in participants who received mRNA-1345 sequentially with Fluzone HD. For each of the 4 influenza strains, the noninferiority in the GMT in participants who received mRNA-1345 coadministered with Fluzone HD compared with that of participants who received mRNA-1345 sequentially with Fluzone HD will be demonstrated by the LB of the 95% CI of the GMR of ruling out 0.667 (i.e., LB >0.667), using a noninferiority margin of 1.5. The GMR is the ratio of the GMT of anti-HA Abs in participants who received mRNA-1345 coadministered with Fluzone HD compared with the GMT of anti-HA Abs in participants who received mRNA-1345 sequentially with Fluzone HD.

**Secondary Objective to Evaluate the Impact on the Immune Response to RSV-A:**

Secondary endpoints based on SRR 21 days after mRNA-1345 administration:

The null hypothesis $H_0^7$: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Fluzone HD, as measured by SRR of RSV-A nAbs at Day 22 (Arm 1), is inferior compared with that in participants who received mRNA-1345 sequentially with Fluzone HD, as measured by SRR of RSV-A nAbs at Day 43 (Arm 2). The noninferiority in the SRR in participants who received mRNA-1345 coadministered with Fluzone HD compared with that of participants who received mRNA-1345 sequentially with Fluzone HD will be demonstrated by the LB of the 95% CI of the SRR difference of ruling out -10% (i.e., LB >-10%), using a noninferiority margin of 10%. The SRR difference is the SRR of RSV-A nAb in participants who received mRNA-1345 coadministered with Fluzone HD minus the SRR of RSV-A nAbs in participants who received mRNA-1345 sequentially with Fluzone HD.

**Secondary Objective to Evaluate the Impact on the Immune Response to RSV-B:**

Secondary endpoints based on SRR 21 days after mRNA-1345 administration:

The null hypothesis $H_0^8$: immunogenicity response to mRNA-1345 in participants who received mRNA-1345 coadministered with Fluzone HD, as measured by SRR of RSV-B nAbs at Day 22 (Arm 1), is inferior compared with that in participants who received mRNA-1345 sequentially with Fluzone HD, as measured by SRR of RSV-B nAbs at Day 43(Arm 2). The noninferiority in the SRR of RSV-B nAbs in participants who received mRNA-1345 coadministered with Fluzone HD compared with that of participants who received mRNA-1345 sequentially with Fluzone HD will be demonstrated by the LB of the 95% CI of the SRR difference of ruling out -10% (i.e., LB >-10%), using a noninferiority margin of 10%. The SRR difference is the SRR of RSV-B nAb in participants who received mRNA-1345 coadministered with Fluzone HD minus the SRR of RSV-B nAbs in participants who received mRNA-1345 sequentially with Fluzone HD.

**Secondary Objective to Evaluate the Impact on the Immune Response to Influenza Based on Seroconversion From Baseline:**

Secondary endpoint based on SCR 21 days after Fluzone HD administration:

The null hypotheses $H_0^9$ to $H_0^{12}$: immunogenicity response to Fluzone HD in participants who received mRNA-1345 coadministered with Fluzone HD, as measured by SCR of influenza anti-HA Abs for each influenza strain at Day 22 (for both Arm 1 and Arm 2) using HAI assay, is inferior compared with that in participants who received mRNA-1345 sequentially with Fluzone HD. The noninferiority in SCR in participants who received mRNA-1345 coadministered with Fluzone HD compared with that of participants who received mRNA-1345 sequentially with Fluzone HD will be demonstrated by the LB of the 95% CI of the SCR difference of ruling out -10% (i.e., LB >-10%) using a noninferiority margin of 10%. The SCR difference is the SCR of anti-HA Abs in participants who received mRNA-1345 coadministered with Fluzone HD minus the SCR of anti-HA Abs in participants who received mRNA-1345 sequentially with Fluzone HD.

Hypotheses 7 to 12 will be assessed once all the primary hypotheses (i.e., hypothesis 1 to 6) are demonstrated.

### 4.3. Sample Size and Power

The study will plan to randomize approximately 1900 participants in a 1:1 ratio, with approximately 950 participants receiving Fluzone HD + mRNA-1345 followed by placebo (Arm 1) and 950 participants receiving Fluzone HD + placebo followed by mRNA-1345 (Arm 2).

With approximately 950 participants in each group, the study has approximately 95% probability to observe at least 1 participant with an AE at a true 0.3% AE rate in that group.

Assuming approximately 10% of participants are ineligible to be included in the PP Set, 855 participants will be included in each group. There is at least 98.5% power to demonstrate the noninferiority of the immune response to RSV-A and RSV-B, as measured by GMT of RSV-A and RSV-B nAb at Day 22 (Arm 1) or Day 43 (Arm 2) in participants receiving mRNA-1345 coadministered with Fluzone HD compared with that in mRNA-1345 sequentially administered with Fluzone HD, at a 2-sided alpha of 0.05, assuming a noninferiority margin of 1.5 and an underlying GMR of 0.9. The standard deviation of the natural log-transformed level is assumed to be 1.5.

The global power considered adequate to meet the primary objectives and evaluate the immune responses to RSV-A, RSV-B, and influenza is at least 91.3%. Sample size justification for the coprimary endpoints is shown in Table 2.

**Table 2: Sample Size Justification**

| Coprimary Endpoint | Number of Evaluable Participants (with 10% Ineligible for the PP Set) | α | Standard Deviation | GMR Assumption | NI Margin | Power |
|---|---|---|---|---|---|---|
| **mRNA-1345 Noninferiority (2-sided test)** | | | | | | |
| RSV-A GMT Day 22 (Arm 1) versus Day 43 (Arm 2) | 855 | 0.05 | 1.5 | GMR=0.9 | 1.5 | 98.5% |
| RSV-B GMT Day 22 (Arm 1) versus Day 43 (Arm 2) | 855 | 0.05 | 1.5 | GMR=0.9 | 1.5 | 98.5% |
| **Fluzone HD Noninferiority (2-sided test) for Each Influenza Strain** | | | | | | |
| GMT Day 22 (Arm 1) versus Day 22 (Arm 2) | 855 | 0.05 | 1.5 | GMR=0.9 | 1.5 | 98.5% |
| **Overall power to show noninferiority on both mRNA-1345 and Fluzone HD** | | | | | | 91.3% |

## 4.4. Randomization

The randomization will be in a blinded manner using a centralized Interactive Response Technology (IRT) system, in accordance with pre-generated randomization schedules.

The study will enroll approximately 1900 medically stable adults ≥65 years of age. Participants will be randomized with a ratio of 1:1 to receive either 1) Fluzone HD+mRNA-1345 CCI µg on Day 1 followed by placebo (0.9% sodium chloride) on Day 22 (Arm 1); or 2) Fluzone HD+placebo (0.9% sodium chloride) on Day 1 followed by mRNA-1345 CCI µg on Day 22 (Arm 2). Randomization will be stratified by age (65 to <75 years and ≥75 years [approximately 10%]).

## 4.5. Blinding and Unblinding

This is an observer-blind study. The investigator, study clinic staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the study intervention administered until the study database is locked and unblinded with certain exceptions; please refer to Section 6.4 and Section 9.1 of the protocol and Data Blinding Plan for details.

# 5. Analysis Populations

Analysis populations for statistical analyses are Randomized Set, Full Analysis Set (FAS), Per-protocol (PP) Set, Solicited Safety Set, and Safety Set.

## 5.1. Randomized Set

The Randomized Set includes all participants who are randomized in the study, regardless of the participant's treatment status in the study. Participants will be included in the treatment group to which they are randomized.

## 5.2. Full Analysis Set

The FAS includes all randomized participants who receive any study intervention. Participants will be included in the treatment group to which they are randomly assigned.

## 5.3. Per-protocol Set

The PP Set includes all participants in the FAS who receive the assigned study intervention dose according to protocol, comply with immunogenicity blood sampling to have a baseline and at least 1 postinjection assessment, and have no important protocol deviations that impact the immune response. Important protocol deviations leading to exclusion of participants from the PP set are defined in Section 6.2.7 (Important Protocol Deviations).

The PP Set will be the primary population used for the analysis of immunogenicity data. Participants will be included in the treatment group to which they are randomly assigned.

In the immunogenicity analysis based on the PP Set, immunogenicity assessments falling out of analysis visit window (Appendix B) will be excluded from the analysis.

## 5.4. Safety Set

The Safety Set includes all randomized participants who receive any study intervention.

The Safety Set will be used for all analyses of safety data except for the solicited ARs. Participants will be included in the treatment group corresponding to the study intervention they actually received.

## 5.5. Solicited Safety Set

The Solicited Safety Set includes all randomized participants who receive any study intervention and contribute any solicited ARs data, i.e., have at least one post-baseline solicited safety assessment. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the treatment group corresponding to the study intervention they actually received.

In addition, 2 subsets of the Solicited Safety Set are defined for Day 1 injection and Day 22 injection. Day 1 (Day 22) Solicited Safety Set consists of all participants in the Solicited Safety Set who have received the study injection on Day 1 (Day 22) and have contributed any solicited AR data from the time of study injection on Day 1 (Day 22) through the following 6 days.

# 6. Statistical Analysis

## 6.1. General Considerations

The Schedule of Activities is provided in Appendix F.

**Continuous variables** will be summarized using the following descriptive summary statistics: the number of participants (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). For the summary statistics of all numerical variables, unless otherwise specified, the display precision will follow programming standards. Please see Appendix A for variable display standards.

**Categorical variables** will be summarized using counts and percentages. When count data are presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of participants in that treatment group within the analysis set of interest, unless otherwise specified.

**Baseline value** is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the Day 1 injection, unless otherwise specified. For immunogenicity assessments, the baseline is defined as the following:

- Influenza Abs for all participants randomized to Study Arm 1 or Arm 2: The baseline is defined as the most recent non-missing result/measurement (scheduled or unscheduled) collected before or on the date of the Day 1 injection.
- RSV Abs for participants randomized to Study Arm 1: The baseline is defined as the most recent non-missing result/measurement (scheduled or unscheduled) collected before or on the date of the Day 1 injection.
- RSV Abs for participants randomized to Study Arm 2: The baseline is defined as the most recent non-missing result/measurement (scheduled or unscheduled) collected before or on the date of the Day 22 injection.

**Study day relative to the Day 1 injection** will be calculated as below:

a) Study day prior to the Day 1 injection will be calculated as: date of assessment/event – date of the Day 1 injection (resulting in negative study day).

b) Study day on or after the date of the Day 1 injection will be calculated as: date of assessment/event – date of the Day 1 injection + 1.

**Study day relative to the most recent injection** will be calculated as below:

a) Study day prior to the Day 1 injection will be calculated as: date of assessment/event – date of the Day 1 injection;

b) Study day on or after the date of the Day 1 injection but before the Day 22 injection (if applicable) will be calculated as: date of assessment/event – date of the Day 1 injection + 1;

c) Study day on or after the date of the Day 22 injection will be calculated as: date of assessment/event – date of the Day 22 injection + 1; if study day is on the same day as the Day 22 injection, date and time will be compared with the Day 22 injection date and time. If it is prior to the Day 22 injection, then study day is calculated as bullet point b); if it is after the Day 22 injection or the time is missing or not available then study day is calculated as: date of assessment/event – date of the Day 22 injection + 1.

**For GMT and GMC calculation**, antibody values reported as below the LLOQ will be replaced by 0.5 × LLOQ and antibody values greater than the ULOQ will be converted to the ULOQ.

**Unscheduled visits:** Unscheduled visit measurements will be included in analysis as follows:

- In the derivation of baseline measurements.
- In scheduled visit windows per specified visit windowing rules.
- In individual participant data listings as appropriate.

**Visit windowing rules:** The analysis visit windows for protocol-defined visits are provided in Appendix B.

**Incomplete/missing data:**

- Imputation rules for missing dates of prior/concomitant medications and non-study vaccinations are provided in Appendix C.
- Imputation rules for missing dates of prior/concomitant procedures are provided in Appendix D.
- Imputation rules for missing AE dates are provided in Appendix E.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

**Treatment groups:**

The following treatment groups will be used for summary purposes:

- D1: Fluzone HD+mRNA-1345 (CCI µg) and D22: placebo
- D1: Fluzone HD+placebo and D22: mRNA-1345 (CCI µg)

If a subject receives any dose of mRNA-1345 on Day 1, regardless of the treatment group the subject is randomized to, the subject will be included in the actual treatment group "D1: Fluzone HD+mRNA-1345 (CCI µg) and D22: placebo" for safety and reactogenicity analyses.

All analyses and data summaries/displays for disposition, demographics and baseline characteristics, safety and immunogenicity will be provided by treatment group using appropriate analysis population, unless otherwise specified. Local solicited adverse reactions will be also summarized by injection content (mRNA-1345, Placebo and Fluzone HD).

## 6.2. Background Characteristics

### 6.2.1. Participant Disposition

The number and percentage of participants in the following categories (analysis sets defined in Section 5) will be summarized by treatment group as defined in Section 6.1 based on Randomized Set:

- Randomized Set
- Full Analysis Set
- Per-protocol Set
- Safety Set
- Solicited Safety Set
  - Day 1 Solicited Safety Set
  - Day 22 Solicited Safety Set

The percentages will be based on the number of participants in the Randomized Set (as randomized), except that for the Safety Set and Solicited Safety Set in which the percentages will be based on the number of participants in the Safety Set (as treated).

The number of participants in the following categories will be summarized based on participants screened:

- Number of participants screened
- Number and percentage of screen failure participants and the reason for screen failure

The percentage of participants who screen failed will be based on the number of participants screened. The percentage of participants reporting each reason for screen failure will be based on the number of participants who screen failed.

The number and percentage of participants in each of the following disposition categories will be summarized by treatment group based on the Randomized Set:

- Received Day 1 injection
- Received Day 22 injection
- Prematurely discontinued before receiving the Day 22 injection and the reason for discontinuation
- Completed the study
- Prematurely discontinued the study and the reason for discontinuation

The number and percentage of participants by IRT randomized stratum (65 to <75 years and ≥75 years) will be presented by treatment group. Also, the concordance between IRT randomized stratum and CRF derived stratum will be tabulated by treatment group.

A participant disposition listing will be provided, including informed consent, participants who completed the study injection schedule, participants who completed study, participants who discontinued from study vaccine or who discontinued from participation in the study, with reasons for discontinuation. A separate listing will be provided for screen failure participants with reasons for screen failure.

A participant, who has completed all periods of the study, including the last visit or scheduled procedure (i.e., 6 months after administration of the Day 22 injection), is considered to have completed the study.

### 6.2.2. Demographics and Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics:

- Age (years)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) ($kg/m^2$)

The number and percentage of participants will be provided for following categorical variables:

- Randomized age group (65 to <75 years, ≥75 years)
- Actual age group (65 to <75 years, ≥75 years)
- Gender (Male, Female)

- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Not Reported, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)

The summaries will be presented by treatment group as defined in Section 6.1. The summaries will be provided separately based on the Randomized Set, FAS, Safety Set, and PP Set.

For screened failure participants, age (years), as well as gender, race, ethnicity will be presented in a listing.

In addition, participants with any inclusion and exclusion criteria violation will also be provided in a listing.

### 6.2.3. Medical History

Medical history data will be coded by system organ class (SOC), high level group term (HLGT) (for selected medical conditions), and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA, version 25.0 or higher).

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of the "D1: Fluzone HD+mRNA-1345 (CCI µg) and D22: placebo" group and then alphabetically within SOC.

Number of events and number of participants with selected medical conditions of clinical interest, as indicated in Appendix I, will also be summarized by SOC, HLGT, and PT for each treatment group.

Medical history data and selected medical conditions of clinical interest will be presented in a listing separately.

### 6.2.4. Prior and Concomitant Medications

Any medication or vaccine (including OTC or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study will be recorded in the participant's eCRF. Specific categories of interest are detailed in the section 6.9 of the study protocol.

Prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary (WHO-DD). The summary of concomitant medications will be based on the Safety Set. Imputation rules for missing/partial dates for medications is detailed in Appendix C.

For analysis purpose, a medication taken prior to the Day 1 injection date, regardless of whether the end date is before or after the injection date, is defined as "prior"; if the medication is taken on or after the Day 1 injection date through Month 6/EoS visit , then it is considered "concomitant", regardless of whether the start date is before or after the injection date.

An overall summary table of concomitant medications and non-study vaccinations will be provided to present the number and percentage of participants who take the following:

- Any concomitant medications and non-study vaccinations within 7 days post any injection
- Any concomitant medications and non-study vaccinations within 21 days post any injection
- Any non-study vaccinations within 7 days post any injection
- Any non-study vaccinations within 21 days post any injection
- Any prophylactic antipyretics or analgesics medication within 21 days post any injection
- Any antipyretic or analgesic medication within 21 days post any injection

A summary table of concomitant medications and non-study vaccinations within 21 days post any injection will be provided by ATC level 2 and PT. PT will be displayed in descending order of frequency of the "D1: Fluzone HD+mRNA-1345 (ECU µg) and D22: placebo" group. A separate summary table of non-study vaccinations within 7 days post any injection will be also provided by PT.

An overall summary of medications taken to prevent or treat fever or pain within 7 days post each injection will be also provided by treatment group based on Day 1 (Day 22) Solicited Safety Set. The summary will be based on participants' responses to the eDiary questions regarding whether they have taken any antipyretic or analgesic medications to prevent or treat fever/pain within 7 days post injection.

Prior, concomitant and non-study vaccinations will be presented in a listing.

### 6.2.5. Concomitant Procedures/Surgeries

Procedures and/or surgeries data will be coded by SOC and PT using the MedDRA. Imputation rules for missing/partial dates of procedures/surgeries are detailed in Appendix D.

For analysis purpose, a procedure/surgery occurred prior to the injection date (including cases where the procedure/surgery date is completely missing) is defined "prior"; if the procedure/surgery is performed on or after the Day 1 injection date through Month 6/EoS visit, then it is considered "concomitant".

The number and percentage of participants with any concomitant procedure/surgery within 21 days post any injection will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple procedures/surgeries within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of the "D1: Fluzone HD+mRNA-1345 (CCI µg) and D22: placebo" group and then alphabetically within SOC.

Concomitant procedures/surgeries will be presented in a listing.

### 6.2.6. Study Exposure

The number and percentage of participants received vaccine injection at Day 1 visit, Day 22 visit as well as the study duration from the Day 1 injection to the EoS will be summarized by treatment group and overall for Safety Set and PP Set. Study injection detail as well as participant with dosing error will be presented in a listing.

### 6.2.7. Important Protocol Deviations

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. Important protocol deviations will be identified based on the protocol at the start of the study and updated during the conduct of the study, and will be finalized before database lock (DBL).

The number and percentage of the participants with any important protocol deviations in each category will be provided by treatment group based on the Randomized Set.

A subset of important protocol deviations, which impact critical or key study data and thus lead to exclusion of participants from the PP set, may include (but are not limited to) the following:

- Received a wrong Day 1 study intervention or Day 22 study intervention
- Enrolled/dosed at two investigational sites
- Did not have a baseline immunogenicity assessment
- Did not have any postinjection immunogenicity assessment
- Received prohibited medication (s) affecting immune responses

The important protocol deviations leading to exclusion from the PP set will be determined and documented by Sponsor prior to DBL and unblinding. Reasons of exclusion from PP Set for immunogenicity will be summarized by treatment group.

Significant protocol deviations will be presented in a listing.

### 6.2.8. COVID-19 Impact

An individual data listing on COVID-19 impact will be provided for the Randomized Set and it will include which visit(s)/assessment(s) has (have) been missed due to COVID-19, along with the specific relationship to COVID-19.

## 6.3. Safety Analysis

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic), unsolicited AEs, SAEs, MAAEs, AESI, AEs leading to withdrawal from study vaccine and/or study participation, vital signs, and physical examination findings. Solicited ARs will be coded according to the MedDRA for AR terminology and unsolicited AEs will be coded by SOC and PT according to the MedDRA (version 25.0 or higher). The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) will be used in this study.

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by treatment group as defined in Section 6.1, unless otherwise specified.

### 6.3.1. Solicited Adverse Reactions

An AR is any AE for which there is a reasonable possibility that the test product caused the AE. The term “Solicited Adverse Reactions” refers to selected signs and symptoms occurring after each injection administration during a specified post-injection follow-up period (day of injection and 6 subsequent days). The solicited ARs are recorded by the participant in eDiary. The eDiary will solicit daily participant reporting of ARs using a structured checklist (Section 8.3.3 of the study protocol). Participants will record such occurrences in an eDiary from Day 1 through Day 7 (i.e., the day of injection and 6 subsequent days). Local solicited ARs will be recorded separately for each injection site (left and right arm). Severity grading of reactogenicity will occur automatically based on participant entry in the eDiary according to the grading scales presented in Table 7 of the study protocol, which are modified from the toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (DHHS 2007). All solicited ARs (local and systemic) reported in the eDiary will be considered causally related to study injection.

If a participant had a Grade 1 or higher AR during the solicited period and did not record the event in the eDiary, the event should be recorded on the Reactogenicity eCRF. If the event starts during the solicited period, but continues beyond 7 days after dosing, the participants should notify the site to provide an end date and close out the event on the Reactogenicity eCRF. If the participant reported an event that started after the solicited period (i.e., beyond 7 days after

dosing), it should be recorded as an AE on the AE eCRF. Causality for these events will be determined per assessment by the Investigator.

The following local ARs for each injection site (left and right arm) will be solicited by the eDiary: injection site pain, injection site erythema (redness), injection site swelling/induration (hardness), and axillary (underarm) swelling or tenderness ipsilateral to the injection arm. The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aches in several joints), nausea/vomiting, chills, and fever.

All analyses of solicited ARs will be provided separately after Day 1 injection and Day 22injection by treatment group as defined in Section 6.1 based on the Day 1 (Day 22) Solicited Safety Set. Summaries of local solicited ARs will be also presented by treatment group and injection content (mRAN-1345, Fluzone HD, and Placebo).

The number and percentage of participants with any solicited ARs, any solicited local ARs and any solicited systemic ARs during the 7-day follow-up period after each injection will be summarized by treatment group with a 2-sided 95% exact CI using the Clopper-Pearson method. Refer to Safety Estimand 3a in Appendix G, Table 6.

The following summaries for solicited ARs will be presented by treatment group:

- The number and percentage of participants who reported any solicited ARs, any solicited local ARs and any solicited systemic ARs within 30 minutes after each injection.
- The number and percentage of participants who reported each individual solicited AR (has a severity grade of Grade 1 or greater) during the 7-day follow-up period after each injection will be summarized by severity grade. For each local solicited AR after Day 1 injection, the summary will be based on the highest grade of the ARs observed from both injection sites (left and right arm).
- The number and percentage of participants who reported each individual solicited AR will be summarized by the onset day relative to the corresponding injection (Day 1 through Day 7). The onset day of an individual solicited AR is defined as the time point after each injection at which the respective solicited AR first occurred. For each local solicited AR after Day 1 injection, the summary will be based on the earliest onset day of the ARs from both injection sites (left and right arm).
- The duration (days) of each individual solicited AR will be summarized descriptively for each injection. The duration will be calculated as: end date of solicited AR event – reaction start date of solicited AR event +1, no matter if it is intermittent or continued or if the solicited AR continues beyond 7 days. For each local solicited AR after Day 1

injection, the summary will be based on the longest duration of the ARs observed from both injection sites (left and right arm).

- The number and percentage of participants who reported each individual solicited AR that continue beyond 7 days post-injection will be summarized for each injection.

The number and percentage of participants who reported each individual solicited AR after each injection summarized by severity grade and by onset day will be also presented separately for local solicited ARs only by treatment group and injection content.

Bar plots may be created to display the percentage of participants who reported solicited AR after each injection.

The summaries of solicited ARs by treatment group and local solicited ARs by treatment group and injection content may be provided for the following subgroup:

- Age group (65 to <75 years, ≥75 years)
- Sex (Male, Female)
- Race (White, Black, Asian, Other [including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and other races])
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

These summaries may be provided for additional subgroups of selected baseline characteristics. If the number of participants in certain subgroups are too small, it may be combined with the other subgroups for the subgroup analyses.

### 6.3.2. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. AEs will also be evaluated by the investigator for the coexistence of MAAE which is defined as an AE that leads to an unscheduled visit to a healthcare practitioner (HCP).

For analysis purpose, an AE is defined as any event occurring during the study but not present before exposure to study vaccine. Worsening of a pre-existing condition after vaccination will be reported as a new AE.

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR but starts outside the protocol-defined period for

reporting solicited ARs (i.e., 7 days after each study injection). For analysis and reporting purpose, unsolicited AEs will include the following:

- AEs that are reported by participants and recorded on the AE eCRF
- Solicited ARs that meet SAE criteria or last beyond 7 days after each injection and are recorded on the Reactogenicity eCRF

Unsolicited AEs will be collected for up to 21 days after each injection; SAEs, MAAEs, AESIs, and AEs leading to study discontinuation will be collected throughout the study. Unsolicited AEs will be summarized up to 21 days separately after Day 1 injection and Day 22 injection unless otherwise specified. Additionally, SAEs, MAAEs, AESIs and AEs leading to study discontinuation will be summarized throughout the study (up to Day 202/EoS). Refer to Safety Estimand 3b in Appendix G, Table 6.

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT (or by PT). SOC will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency in the "D1: Fluzone HD+mRNA-1345 (CCI µg) and D22: placebo" group and then alphabetically within SOC. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once.

For the by-severity summaries, the toxicity grade of a solicited AR meeting SAE criteria or lasting beyond 7 days after each injection will be mapped to a severity level of Mild/Grade 1, Moderate/Grade 2 or Severe/≥ Grade 3 and the maximum severity level in the case of multiple events will be presented.

Percentages will be based upon the number of participants in the Safety Set within each treatment group.

#### 6.3.2.1. Overview of AEs

An overall summary of unsolicited AEs up to 7 days after each injection, between 8 to 21 days after each injection, and up to 21 days after each injection will be provided, for the number and percentage of participants, along with the number of events, by treatment group who experience at least one of the categories:

- Any unsolicited AEs
- Any serious AEs
- Any fatal AEs
- Any unsolicited medically-attended AEs

- Any unsolicited AEs leading to discontinuation from study vaccine
- Any unsolicited AEs leading to study discontinuation
- Any unsolicited severe AEs
- Any unsolicited non-serious AEs (no SAE)
- Any unsolicited non-serious severe AEs (no SAE)
- Any unsolicited non-serious AEs (regardless of SAE)
- Any unsolicited non-serious severe AEs (regardless of SAE)
- Any unsolicited AESI

Note: Severe AEs include both unsolicited severe AEs and ≥Grade 3 solicited ARs that meet SAE criteria or last beyond 7 days after each injection.

Summary tables will also be provided to include number and percentage of participants with unsolicited AEs that are treatment-related in each of the above categories.

Additionally, the overall summary for the categories of SAEs, MAAEs, AESIs, and AEs leading to study discontinuation will be provided for these AEs throughout the study.

Separate listings containing individual participant AE data throughout the study for AEs, treatment-related AEs, serious AEs, serious treatment-related AEs, medically-attended AEs, treatment-related medically-attended AEs, AEs leading to discontinuation from study vaccine, AEs leading to study discontinuation, severe AEs, treatment-related severe AEs, AESIs, and fatal AEs will be provided.

Listing of deaths, including cause of death, will be provided.

#### 6.3.2.2. AEs by System Organ Class and Preferred Term

The following summary tables of unsolicited AEs up to 21 days after each injection will be provided by SOC and PT using frequency counts and percentages (i.e., number and percentage of participants with an event):

- All unsolicited AEs
- All unsolicited AEs that are treatment-related
- All serious AEs
- All serious AEs that are treatment-related
- All unsolicited non-serious AEs (regardless of SAE)
- All unsolicited non-serious severe AEs (regardless of SAE)

- All unsolicited medically-attended AEs
- All unsolicited medically-attended AEs that are treatment-related
- All unsolicited AEs leading to discontinuation from study vaccine
- All unsolicited AEs leading to study discontinuation
- All unsolicited severe AEs
- All unsolicited severe AEs that are treatment-related
- All unsolicited treatment emergent AESI

Note: Severe AEs include both unsolicited severe AEs and ≥Grade 3 solicited ARs that meet SAE criteria or last beyond 7 days after each injection.

Summary tables by SOC and PT will also be provided for number and percentage of participants with unsolicited AEs up to 7 days after each injection, and between 8 to 21 days after each injection.

Additionally, summary tables of SAEs, treatment-related SAEs, MAAEs, treatment-related MAAEs, AEs leading to study discontinuation, and AESIs will be also provided by SOC and PT considering all events reported throughout the study.

#### 6.3.2.3. AEs by Preferred Term

A summary table for all unsolicited AEs up to 21 days after each injection will be provided by PT in descending order of frequency in the "D1: Fluzone HD+mRNA-1345 (CCI µg) and D22: placebo" group.

#### 6.3.2.4. AEs by Severity

The following summary tables of AEs up to 21 days after each injection will be provided by the severity, SOC and PT using frequency counts and percentages:

- All unsolicited AEs
- All unsolicited AEs that are treatment-related

Summary tables of unsolicited AEs up to 21 days after each injection with occurrence in ≥ 1% of participants in any treatment group based on preferred term will be also provided by severity, SOC and PT.

#### 6.3.2.5. AEs by SMQ

The number of events and number of participants reported occurrence of selected AEs of clinical interests identified by SMQs up to 7 days after each injection, up to 21 days after each injection, and throughout the study will be summarized by SMQ, subordinate SMQ, and PT. Two sets of

summary tables will be provided, one will be based on combined broad and narrow scope of SMQ, the other will be based on narrow scope. SMQ and subordinate SMQ within each SMQ will be displayed in alphabetic order. PT will be displayed in descending order of number of participants in "D1: Fluzone HD+mRNA-1345 (CCI µg) and D22: placebo" group and then alphabetically within subordinate SMQ or SMQ if no subordinate SMQ. Detail information for the selected SMQ is presented in Appendix H Table 7 and Table 8.

Selected AEs of clinical interests identified by SMQs up to 21 days after each injection and throughout the study will be provided in listings.

#### 6.3.2.6. AEs by System Organ Class, High Level Group Term, and Preferred Term

Certain AEs, as indicated in Appendix I, will also be summarized by SOC, HLGT, and PT for each treatment group and presented by three time periods: up to 7 days after each injection, up to 21 days after each injection, and throughout the study.

#### 6.3.2.7. Independent Cardiac Event Adjudication Committee (CEAC)

An independent CEAC of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (see more details in Section 10.1.6.2 of the protocol) and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review can be found in the CEAC charter.

A summary table will be provided based on the data adjudicated by the CEAC, as the primary analysis of cardiac events.

Cardiac events adjudicated by the CEAC will be provided in a listing.

#### 6.3.2.8. Subgroup Analysis of AEs

The overview of AEs, AEs by SOC/PT, AEs by Severity, unsolicited treatment-related AEs by SOC/PT and serious AEs by SOC/PT may be provided for the following subgroup:

- Age group (65 to <75 years, ≥75 years)
- Sex (Male, Female)

- Race (White, Black, Asian, Other [including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and other races])
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

These summaries may be provided for additional subgroups of selected baseline characteristics. If the number of participants in certain subgroups are too small, it may be combined with the other subgroups for the subgroup analyses.

### 6.3.3. Vital Sign Measurements

Vital signs will only be collected at Screening and on the day of injection (Day 1 and Day 22), once before and at least 30 minutes after each injection. Vital signs will be collected at other study visits only in conjunction with a symptom-directed physical examination.

Vital sign measurements, including systolic and diastolic blood pressures, pulse rate, respiratory rate and body temperature will be presented in a data listing. The values meeting the toxicity grading criteria (DHHS 2007) will be flagged in the data listing.

For each injection (Day 1 or Day 22), the observed pre-injection and post-injection values and change from pre-injection to post-injection will be summarized by treatment group. Shift from pre-injection to post-injection in the toxicity grades for each injection will also be summarized by treatment group.

The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any vital sign measurement will be listed separately. If a participant has a vital sign result with Grade 2 or higher abnormality at any post injection visit, then all results of that specific vital sign for that participant will be presented in the listing.

## 6.4. Immunogenicity Analysis

The analyses of immunogenicity will be using the PP Set, by treatment group. The supportive analyses of immunogenicity especially for primary immune response will be conducted using the FAS based on Appendix G. If the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, additional supportive analyses of non-primary immunogenicity may be conducted using the FAS.

The GMT, GMC, and GM level will be calculated using the following formula:

$$10^{\left\{\frac{1}{n}\sum_{i=1}^{n}\log_{10}(y_{it})\right\}}$$

where $y_{1t}, y_{2t}, \cdots, y_{nt}$ are $n$ observed immunogenicity titers or levels for participants $i=1, 2, \ldots, n$ at time point $t$.

The GMFR measures the changes in immunogenicity titers or levels from baseline within participants. The GMFR will be calculated using the following formula:

$$10^{\left\{\frac{1}{n}\sum_{i=1}^{n}\log_{10}\left(\frac{y_{it}}{y_{i0}}\right)\right\}} = 10^{\left\{\frac{1}{n}\sum_{i=1}^{n}[\log_{10}(y_{it})-\log_{10}(y_{i0})]\right\}}$$

where $y_{1t}, y_{2t}, \cdots, y_{nt}$ are observed immunogenicity titers or levels for participants i's at time point t. and $y_{10}, y_{20}, \cdots, y_{n0}$ are immunogenicity titers or levels for participants i's at time point 0 (baseline).

### 6.4.1. Immunogenicity Assessments

Immunogenicity assessments will include the following:

- Serum RSV-A and RSV-B nAbs as measured by microneutralization assay
- Serum anti-HA Abs for each influenza strain (A/H1N1, A/H3N2, B/Yamagata, B/Victoria) as measured by HAI assay

RSV binding antibody levels may be presented as appropriate.

### 6.4.2. Analysis of the Primary Immunogenicity Endpoints

The coprimary endpoints will be analyzed on the PP Set in order to estimate Estimands 1a-2a (refer to Appendix G, Table 5). In addition, this will be supported by estimation of a treatment policy Estimand (Estimands 1b-2b) on the FAS Set.

#### 6.4.2.1. Primary Analysis Approach

The coprimary endpoints include the following:

- GMT of serum RSV-A and RSV-B nAbs at Day 22 (Arm 1) and Day 43 (Arm 2)
- GMT of serum influenza anti-HA Abs as measured by HAI assay at Day 22

The statistical analyses are:

- For each coprimary endpoint, the GMR will be estimated using an analysis of covariance (ANVOVA) model on the log-transformed titers, with the treatment group and log-transformed baseline titers as the fixed covariate, adjusted for stratified age group used for randomization. The geometric least square mean (GLSM) for each treatment group and its corresponding 95% CI in a log-transformed scale will be estimated from the model and back-transformed to obtain these estimates in the original scale as an estimate of the GMT and its 95% CI. The GMR estimated by the ratio of the GLSMs and the corresponding 2-sided 95% CI will be provided to assess the treatment difference in the immune response between the 2 treatment groups. For each coprimary endpoint, the

noninferiority of the GMT will be demonstrated if the LB of the 95% CI of the GMR is >0.667 based on a noninferiority margin of 1.5.

- Additionally, GMT of RSV-A nAb, RSV-B nAb, and influenza anti-HA Abs for each influenza strain with corresponding 95% CI will be provided at each visit (as applicable) by treatment group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values and then back transformed to the original scale for presentation. The following descriptive statistics will also be provided at each visit: the number of participants (n), median, minimum and maximum. GMT with 95% CI will be plotted at each visit (as applicable) by treatment group.

The study is considered to meet the primary immunogenicity objective if the noninferiority of the immune response to mRNA-1345 coadministered with Fluzone HD is met based on all the coprimary endpoints.

The above analysis corresponds to the Primary Immune Estimands 1a-2a as described in Appendix G, Table 5.

#### 6.4.2.2. Sensitivity Analysis

Analyses of the primary endpoints will be performed based on the FAS, using the same method and same definition as described in Section 6.4.2.1.

This sensitivity analysis corresponds to the Supportive Immune Estimands 1b-2b as described in Appendix G, Table 5.

### 6.4.3. Analysis of the Secondary Immunogenicity Endpoints

The secondary endpoints include the following:

- SRR in RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2)
- GMFR of RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2) compared to baseline (Day 1 for Arm 1 or Day 22 for Arm 2)
- Proportion of participants with ≥2-fold increase in RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2) compared to baseline (Day 1 for Arm 1 or Day 22 for Arm 2)
- SCR in influenza anti-HA Abs for each influenza strain at Day 22
- GMFR of influenza anti-HA Abs for each influenza strain at Day 22 compared to baseline (Day 1)

The statistical analyses are:

- SRR in RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2) will be provided with 2-sided 95% CIs by treatment group using the Clopper-Pearson method. The SRR

difference between the two treatment groups will be provided with 2-sided 95% CIs using the Miettinen-Nurminen's method. For each RSV subtype, the noninferiority of the SRR will be demonstrated if the LB of the 95% CI of the SRR difference is >-10% based on the noninferiority margin of 10%.

- SCR in influenza anti-HA Abs for each influenza strain at Day 22 will be provided with 2-sided 95% CIs by treatment group using the Clopper-Pearson method. The SCR difference between the two treatment groups will be provided with 2-sided 95% CIs using the Miettinen-Nurminen's method. For each influenza strain, the noninferiority of the SCR will be demonstrated if the LB of the 95% CI of the SCR difference is >-10% based on the noninferiority margin of 10%.
- GMFR of RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2) compared to baseline (Day 1 for Arm 1 or Day 22 for Arm 2), and GMFR of influenza anti-HA Abs at Day 22 compared to baseline (Day 1) will be provided with corresponding 95% CI by treatment group. The 95% CIs will be calculated based on the t-distribution of the difference in the log-transformed values (postbaseline time point – baseline) and then back transformed to the original scale for presentation. GMFR with 95% CI will be plotted by treatment group.
- Proportion of participants with ≥2-fold increases in RSV-A and RSV-B nAbs at Day 22 (Arm 1) and Day 43 (Arm 2) compared to baseline (Day 1 for Arm 1 and Day 22 for Arm 2) will be provided with 2-sided 95% CIs by treatment group using the Clopper-Pearson method.

### 6.4.4. Analysis of Exploratory Immunogenicity Endpoints

The exploratory immunogenicity endpoints include the following:

- GMC and GMFR of postinjection/baseline concentration of RSV bAbs
- Proportions of participants with ≥2-fold and ≥4-fold increases in RSV bAb concentration postinjection

The following analyses may be performed:

- GMC and GMFR of RSV bAbs will be summarized descriptively in the same way as specified in Section 6.4.2.1 and Section 6.4.3.
- Proportions of participants with ≥2-fold and ≥4-fold increases in RSV bAb concentration will be summarized descriptively in the same way as specified in Section 6.4.3.

Similar definition and analysis as SRR of RSV nAbs may also be applied on SRR of RSV bAbs.

### 6.4.5. Subgroup Analysis

All the above specified immunogenicity analyses may be performed by the following subgroup as applicable:

- Age group (65 to <75 years, ≥75 years)
- Sex (Male, Female)
- Race (White, Black, Asian, Other [including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and other races])
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

All the above specified immunogenicity analyses may be performed for additional subgroups of selected baseline characteristics. If the number of participants in certain subgroups are too small, it may be combined with the other subgroups for the subgroup analyses.

## 6.5. Multiplicity Adjustment

A sequential/hierarchical testing procedure will be used to control the overall Type 1 error rate at 0.05 (2-sided) over the primary endpoints, and secondary endpoints.

The coprimary endpoints will be tested at the planned primary analysis at a 2-sided Type 1 error rate of 0.05. The success criteria of all 6 coprimary endpoints need to be met in order to declare the study a success to achieve noninferiority of coadministration.

The secondary endpoints on SRR and SCR will only be tested at the primary analysis at a 2-sided Type 1 error rate of 0.05 when all coprimary endpoints have achieved statistical significance. The secondary endpoints will be tested sequentially in the following order: 1) SCR of influenza anti-HA Abs for each influenza strain, 2) SRR of RSV-A nAbs and 3) SRR of RSV-B nAbs.

No further testing will be performed once the sequence/hierarch breaks, that is, further testing stops as soon as an endpoint in the sequence fails to meet success criterion of noninferiority. Analyses of remaining other secondary immune endpoints are not controlled for multiplicity.

## 6.6. Planned Analyses

The following analyses will be conducted on cleaned data:

1. The primary analysis of safety and immunogenicity data will be performed after all participants have completed Day 43 visit. All data relevant to the primary study analysis through the Day 43 Visit will be cleaned and locked for the primary analysis (i.e., data that are as clean as possible) and a report may be generated. The primary analysis will be performed by a separate team of unblinded programmers and statisticians.

2. The final analysis of all endpoints will be performed after all participants have completed Day 202/EoS. Results of this analysis will be presented in a final CSR.

## 7. Changes from Planned Analyses in Protocol

The following changes from planned analyses in the study protocol are included in this document:

- Appendix G Estimands and Estimand Specification: Estimands language has been added for primary immune endpoint and primary safety endpoint.

## 8. References

Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985; 4:213-226.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007[cited 2022 Jan 11]. Available from: https://www.fda.gov/media/73679/download.

# 9. List of Appendices

## 9.1. Appendix A Standards for Variable Display in TFLs

**Continuous Variables**: The precision for continuous variables will be based on the precision of the data itself. The mean and median will be presented to one more significant figure than the original results; the SD will be presented to two more significant figures than the original results; the minimum and maximum will be presented to the same precision as the original results.

**Categorical Variables**: Percentages will be presented to 1 decimal place. If the count is 0, the percentage will not be displayed. If the count equals the denominator, the percentage will be displayed as 100.

## 9.2. Appendix B Analysis Visit Windows

Analysis visit windows will be utilized for immunogenicity assessments only.

Data will be mapped using the following approach:

Step 1: If the assessments are collected at a scheduled visit, the collected data will be mapped to the nominal scheduled visit.

Step 2: If the assessments are collected at an unscheduled visit or early termination visit, the collected data will be mapped using the analysis visit windows described in Table 3.

If a subject has multiple assessments within the same analysis visit, the following rule will be used:

- If multiple assessments occur within a given analysis visit, the assessment closest to the target study day will be used.
- If there are 2 or more assessments equal distance to the target study day, the last assessment will be used.

**Table 3: Analysis Visit Windows for Immunogenicity Assessments**

| Study Arm | Visit | Visit Window in Study Day | Relative Date |
|---|---|---|---|
| **RSV nAbs and bAbs** | | | |
| Arm 1 | Day 1 | 1 | Date of Day 1 Injection |
| Arm 1 | Day 22 | [15, 36] | Date of Day 1 Injection |
| Arm 2 | Day 22 | 1 | Date of Day 22 Injection |
| Arm 2 | Day 43 | [15, 36] | Date of Day 22 Injection |
| **Influenza anti-HA Abs by HAI assay** | | | |
| Arm 1 and Arm 2 | Day 1 | 1 | Date of Day 1 Injection |
| Arm 1 and Arm 2 | Day 22 | [15, 36] | Date of Day 1 Injection |

## 9.3. Appendix C Imputation Rules for Missing Dates of Prior/Concomitant Medications

Imputation rules for missing or partial start/stop dates of medication are defined below:

1. Missing or partial medication start date:
   - If only Day is missing, use the first day of the month, unless:
   - The medication end date is on/after the date of the injection or is missing/partial AND the start month and year of the medication coincide with the start month and year of the injection. In this case, use the date of the injection.
   - If Day and Month are both missing, use the first day of the year, unless:
   - The medication end date is on/after the date of the injection or is missing/partial AND the start year of the medication coincide with the start year of the IP injection. In this case, use the date of the injection.
   - If Day, Month, and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the injection for purposes of determining if status as prior or concomitant.
2. Missing or partial medication stop date:
   - If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
   - If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
   - If Day, Month, and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

## 9.4. Appendix D Imputation Rules for Missing Dates of Procedures/Surgeries

Imputation rules for missing or partial dates of procedures/surgeries are defined below:

- If only Day is missing, use the first day of the month, unless the start month and year of the procedure/surgery coincide with the start month and year of the injection, in this case, use the date of the injection.
- If Day and Month are both missing, use the first day of the year, unless the start year of the procedure/surgery coincide with the start year of the injection, in this case, use the date of the injection.

- If Day, Month, and Year are all missing, the date will not be imputed, but the procedure/surgery will be treated as concomitant.

## 9.5. Appendix E Imputation Rules for Missing Dates of AEs

Imputation rules for missing or partial start dates and stop dates of AEs are defined below:

1. Missing or partial start date:
   - If only Day is missing, use the first day of the month, unless:
     - The AE end date is on/after the date of the injection or is missing/partial AND the start month and year of the AE coincide with the start month and year of the injection. In this case, use the date of the injection.
   - If Day and Month are both missing, use the first day of the year, unless:
     - The AE end date is on/after the date of the injection or is missing/partial AND the start year of the AE coincides with the start year of the injection. In this case, use the date of the injection.
   - If Day, Month, and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of the injection, then the AE will be considered a pre-treatment AE and will not be included in the AE analyses. Otherwise, the AE will be included in the AE analyses.
2. Missing or partial end dates will not be imputed.

## 9.6. Appendix F Schedule of Activities

| **Study Period** | **Screening** | **Intervention Period** | | | **Follow-up** | | | |
|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **Screening** | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| **Visit Month*** | **-1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** |
| **Visit Day** | **Screening[a]** | **D1[a]** | **D8** | **D22** | **D29** | **D43[b]** | **D91** | **D202/ EoS** |
| **Window Allowance (Days)** | **-28** | **N/A** | **+3** | **+7** | **+3** | **-2 to +7** | **±5** | **±14** |
| **Type of Visit** | **V** | **V** | **SC** | **V** | **SC** | **V** | **SC** | **SC** |
| Informed consent, demographics, concomitant medications and vaccinations, and medical history | X | – | – | – | – | – | – | – |
| Inclusion/exclusion criteria | X | X | – | – | – | – | – | – |
| Physical examination[c] | X | X | – | X | – | – | – | – |
| Vital sign measurements[d] | X | X | – | X | – | – | – | – |
| Randomization | – | X | – | – | – | – | – | – |
| Blood sample collection for humoral immunogenicity[e] | – | X | – | X | – | X | – | – |
| Study vaccination (including a 30-minute postdose observation period)[d,f] | – | X | – | X | – | – | – | – |
| eDiary activation for recording solicited ARs (7 days)[g] | – | X | – | X | – | – | – | – |
| eDiary review[g] | | X | X | X | X | | | |
| Follow-up safety telephone call[h] | – | – | X | – | X | – | X | X |
| Recording of unsolicited AEs | – | X | X | X | X | X | – | – |
| Concomitant medications[i] | – | X | X | X | X | X | – | – |
| Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation, and concomitant medications relevant to or for their treatment[h] | – | X | X | X | X | X | X | X |

| Study Period | Screening | Intervention Period | | | Follow-up | | | |
|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **Screening** | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| **Visit Month*** | **-1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** |
| **Visit Day** | **Screening[a]** | **D1[a]** | **D8** | **D22** | **D29** | **D43[b]** | **D91** | **D202/ EoS** |
| **Window Allowance (Days)** | **-28** | **N/A** | **+3** | **+7** | **+3** | **-2 to +7** | **±5** | **±14** |
| **Type of Visit** | **V** | **V** | **SC** | **V** | **SC** | **V** | **SC** | **SC** |
| Recording of nonstudy vaccinations[h,i] | – | X | X | X | X | X | X | X |
| Study completion | – | – | – | – | – | – | – | X |

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; D = Day; eDiary = electronic diary; EoS = end of study; IM = intramuscular; M = month; MAAE = medically attended adverse event; N/A = not applicable; RSV = respiratory syncytial virus; SAE = serious adverse event; SC = safety telephone call; ; V = in-person visit; – = indicated activity not performed on that day.

*A month is defined as 30 days.

Arm 1: Fluzone HD+mRNA-1345 [CCI] µg on Day 1 followed by placebo (0.9% sodium chloride) on Day 22;

Arm 2: Fluzone HD+placebo (0.9% sodium chloride) on Day 1 followed by mRNA-1345 [CCI] µg on Day 22.

a. The Screening Visit and Day 1 Visit may be performed on the same day or on different days (see protocol Section 5.3 for additional details).

b. If a participant cannot attend a scheduled in-person visit (with the exception of the Screening Visit, Day 1, and Day 22), a home visit is acceptable if performed by appropriately delegated study clinic staff.

c. A complete physical examination, including height and weight, will be performed at the Screening Visit. Symptom-directed physical examinations will be performed at other study visits, if clinically indicated (see protocol Section 8.3.1 for additional details).

d. Vital sign measurements include assessment of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature (preferred route is oral) (see protocol Section 8.3.2 for additional details).

e. Blood samples for humoral immunogenicity must be collected prior to administration of the study intervention on Day 1 and Day 22.

f. All participants will be randomized to receive 2 IM injections, one in each arm, in the deltoid muscle (Day 1) and 1 IM injection in the deltoid muscle (Day 22).

g. At Day 1 and Day 22, eDiary instruction will be provided while the participant is onsite. The participant will be required to make eDiary entries approximately 30 minutes after each vaccination while at the study site and again that same evening when at home. Study participants will continue to record in the eDiary each day at the same time for 6 days following each vaccination. Local solicited ARs will be recorded separately for each injection. eDiary review by the site should occur daily on Day 1-Day 7 and Day 22-28. Additional review of the eDiary will occur at Day 8 and Day 29 between the site and the participant during the safety telephone calls.

h. Medically qualified study staff will contact all participants. The participant will be interviewed according to the script. Information will be collected about occurrence of unsolicited AEs through 21 days postvaccination for either RSV or influenza, and the occurrence of MAAEs, SAEs,

AESIs, or AEs leading to study discontinuation and concomitant medications associated with those events, and receipt of any nonstudy vaccinations at all points of contact.

i. All concomitant medications and procedures will be recorded for 21 days following each vaccination (Day 1 through Day 43); all nonstudy vaccinations and concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded from Day 1 through Month 6 after the last study injection/EoS.

## 9.7. Appendix G Estimands and Estimand Specifications

**Table 4: Intercurrent Events**

| Label | Intercurrent Event Type |
|---|---|
| IcEv1 (Early discontinuation) | Discontinued early from study. |
| IcEv2 (Prohibited medications) | Received any concomitant medications and non-study vaccines deemed to affect immune responses. |
| IcEv3 (Important protocol deviation impacting key study data) | Received a wrong Day 1 study intervention or Day 22 study intervention, enrolled/dosed at two investigational sites, did not have a baseline immunogenicity assessment or did not have any post-injection immunogenicity assessments. |
| IcEv4 (Immunogenicity assessments falling out of visit window) | Had immunogenicity assessments falling out of analysis visit windows described in Appendix B. |

Abbreviation: IcEv: intercurrent event.

**Table 5: Summary of Primary Immune Estimands with Rationale for Strategies to Address Intercurrent Events**

| **Objective: To evaluate the impact of coadministered HD quadrivalent seasonal influenza vaccine on the immune response to mRNA-1345 RSV vaccine against RSV-A and RSV-B** | | |
|---|---|---|
| **Estimand Label** | **Primary Immune Estimand 1a (on the PP Set)** | **Supportive Immune Estimand 1b (on the FAS Set)** |
| **Estimand Description** | Immune response to mRNA-1345 RSV vaccine measured as GMR of RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2) in adults ≥65 years old who receive the assigned study intervention dose at both Day 1 and Day 22, comply with immunogenicity blood sampling to have a baseline and at least 1 postinjection assessment, and have no important protocol deviations impacting the immune response. | Immune response to mRNA-1345 RSV vaccine measured as GMR of RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2) in adults ≥65 years old who receive any study intervention dose irrespective of any important protocol deviations impacting the immune response. |
| **Target Population** | Adults ≥65 years old who receive the assigned study intervention dose at both Day 1 and Day 22, comply with immunogenicity blood sampling to have a baseline and at least 1 postinjection assessment, and have no important protocol deviations impacting the immune response. | Adults ≥65 years old who receive any study intervention dose irrespective of any important protocol deviations impacting immune response. |
| **Endpoint** | GMT of serum RSV-A and RSV-B nAbs at Day 22 (Arm 1) or Day 43 (Arm 2). | As per Estimand 1a. |
| **Treatment Conditions** | Fluzone HD + mRNA-1345/Placebo (Test) vs. Fluzone HD + Placebo/mRNA-1345 (Reference) | As per Estimand 1a. |

| | | |
|---|---|---|
| **Population-Level Summary** | Immune response to mRNA-1345 RSV vaccine defined as GMR of RSV-A and RSV-B nAbs using an ANCOVA model on the log-transformed tiers at Day 22 (Arm 1) or Day 43 (Arm 2), with the treatment group as a fixed variable, adjusted for stratified age group used for randomization and log-transformed baseline tiers. | As per Estimand 1a. |
| **Intercurrent Event Strategy** | | |
| **IcEv1 (Early discontinuation)** | Treatment policy (Including all data collected) | Treatment policy (Including all data collected) |
| **IcEv2 (Prohibited medications)** | Principal stratum (Excluding participants) | Treatment policy (Including all data collected) |
| **IcEv3 (Important protocol deviation impacting key study data)** | Principal stratum (Excluding participants) | Treatment policy (Including all data collected) |
| **IcEv4 (Immunogenicity assessments falling out of visit window)** | Hypothetical (Excluding related data) | Treatment policy (Including all data collected) |
| **Rationale for Strategies** | This estimand seeks to understand immune response impact during the coadministered HD quadrivalent seasonal influenza vaccine in adults aged 65 or older who receive the assigned study intervention dose at both Day 1 and Day 22 and comply with key protocol criteria.<br>A principal stratum is used to exclude participants with prohibited medications affecting immune responses or important protocol deviations impacting key study data so that analysis is a sub-population composed of participants free from such intercurrent events.<br>For early discontinuation, all collected data are included. Immunogenicity assessments falling out of visit window are excluded. | A treatment policy strategy is used for following up immune response including all participants who receive any study intervention dose irrespective of whether they subsequently were found not to strictly meet the key protocol criteria. There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice. |
| **Objective: To evaluate the impact of coadministered mRNA-1345 RSV vaccine on the immune response to HD quadrivalent seasonal influenza vaccine against 4 vaccine-matched influenza A and B strains** | | |
| **Estimand Label** | **Primary Immune Estimand 2a (on the PP Set)** | **Supportive Immune Estimand 2b (on the FAS Set)** |

| | | |
|---|---|---|
| **Estimand Description** | Immune response to HD quadrivalent seasonal influenza vaccine measured as GMR of anti-HA Abs as measured by HAI assay at Day 22 in adults ≥65 years old who receive the assigned study intervention dose at both Day 1 and Day 22, comply with immunogenicity blood sampling to have a baseline and at least 1 postinjection assessment, and have no important protocol deviations impacting the immune response. | Immune response to HD quadrivalent seasonal influenza measured vaccine as GMR of anti-HA Abs as measured by HAI assay at Day 22 in adults ≥65 years old who receive study intervention dose irrespective of any important protocol deviations impacting the immune response. |
| **Target Population** | Adults ≥65 years old who receive the assigned study intervention dose at both Day 1 and Day 22, comply with immunogenicity blood sampling to have a baseline and at least 1 postinjection assessment, and have no important protocol deviations impacting the immune response. | Adults ≥65 years old who receive any study intervention dose irrespective of any important protocol deviations impacting immune response. |
| **Endpoint** | GMT of serum anti-HA Abs by HAI assay at Day 22. | As per Estimand 2a. |
| **Treatment Conditions** | Fluzone HD + mRNA-1345/Placebo (Test) vs.<br>Fluzone HD + Placebo/mRNA-1345 (Reference) | As per Estimand 2a. |
| **Population-Level Summary** | Immune response to HD quadrivalent seasonal influenza vaccine defined as GMR anti-HA Abs by HAI assay using an ANCOVA model on the log-transformed tiers at Day 22, with the treatment group as the fixed variable, adjusted for stratified age group used for randomization and log-transformed baseline tiers. | As per Estimand 2a. |
| **Intercurrent Event Strategy** | | |
| **IcEv1 (Early discontinuation)** | Treatment policy (Including all data collected) | Treatment policy (Including all data collected) |
| **IcEv2 (Prohibited medications)** | Principal stratum (Excluding participants) | Treatment policy (Including all data collected) |
| **IcEv3 (Important protocol deviation impacting key study data))** | Principal stratum (Excluding participants) | Treatment policy (Including all data collected) |
| **IcEv4 (Immunogenicity assessments falling out of visit window)** | Hypothetical (Excluding related data) | Treatment policy (Including all data collected) |

| | | |
|---|---|---|
| **Rationale for Strategies** | This estimand seeks to understand immune response impact during the coadministered HD quadrivalent seasonal influenza vaccine in adults aged 65 or older who receive the assigned intervention dose at both Day 1 and Day 22 and comply with key protocol criteria.<br>A principal stratum is used to exclude participants with prohibited medications affecting immune responses or important protocol deviations impacting key study data so that analysis is a sub-population composed of participants free from such intercurrent events.<br>For early discontinuation, all collected data are included. Immunogenicity assessments falling out of visit window are excluded. | A treatment policy strategy is used for following up immune response including all participants who receive any study intervention dose irrespective of whether they subsequently were found not to strictly meet the key protocol criteria. There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice. |

**Table 6: Summary of Primary Safety Estimands with Rationale for Strategies to Address Intercurrent Events**

| **Objective: To evaluate the safety and tolerability of mRNA-1345 RSV vaccine coadministered with a HD quadrivalent seasonal influenza vaccine (Fluzone® HD)** | | |
|---|---|---|
| **Estimand Label** | **Safety Estimand 3a** | **Safety Estimand 3b** |
| **Estimand Description** | • Proportion of participants reporting any solicited local ARs up to 7 days after each study injection (Day 1 or Day 22).<br>• Proportion of participants reporting any solicited systemic ARs up to 7 days after each study injection (Day 1 or Day 22). | • Proportion of participants reporting any unsolicited AEs up to 21 days after each study injection (Day 1 or Day 22).<br>• Proportion of participants reporting any MAAEs up to Day 202/EOS.<br>• Proportion of participants reporting any AESI up to Day 202/EOS.<br>• Proportion of participants reporting any SAEs up to Day 202/EOS.<br>• Proportion of participants reporting any AEs leading to discontinuation from the study up to Day 202/EOS. |
| **Target Population** | Adults ≥65 years old who receive any study intervention and contribute any solicited AR data. | Adults ≥65 years old who receive any study intervention. |
| **Endpoint** | • Incidence of solicited local ARs up to 7 days after each study injection.<br>• Incidence of solicited systemic ARs up to 7 days after each study injection. | • Incidence of unsolicited AEs up to 21 days after each study injection.<br>• Incidence of MAAEs up to Day 202/EOS.<br>• Incidence of AESI up to Day 202/EOS.<br>• Incidence of SAEs up to Day 202/EOS.<br>• Incidence of AEs leading to discontinuation from the study up to Day 202/EOS. |
| **Treatment Conditions** | Fluzone HD + mRNA-1345/Placebo (Test) vs.<br>Fluzone HD + Placebo/mRNA-1345 (Reference) | Same as Estimand 3a. |

| | | |
|---|---|---|
| **Population-Level Summary** | • Proportion of participants reporting any solicited local ARs up to 7 days after each study injection by treatment group.<br>• Proportion of participants reporting any solicited systemic ARs up to 7 days after each study injection by treatment group. | • Proportion of participants reporting any unsolicited AEs up to 21 days after each study injection by treatment group.<br>• Proportion of participants reporting any MAAEs up to Day 202/EOS by treatment group.<br>• Proportion of participants reporting any AESI up to Day 202/EOS by treatment group.<br>• Proportion of participants reporting any SAEs up to Day 202/EOS by treatment group. |
| **Intercurrent Event Strategy** | | |
| **IcEv1 - IcEv4** | Treatment Policy (Including all data collected) | Treatment Policy (Including all data collected) |
| **Rationale for Strategies** | Count all relevant safety events observed, irrespective of non-compliance of key protocol criteria. | |

## 9.8. Appendix H Definition of AE of Clinical Interest by SMQ

**Table 7: AE of Clinical Interest by SMQ to be Applied**

| SMQ | Broad/Narrow Search | SMQ Search Criteria |
|---|---|---|
| Anaphylactic Reaction | Algorithmic approach | Specified PT and algorithmic approach specified in Table 8 |
| Angioedema | Broad/Narrow | Specified PT |
| Arthritis | Broad/Narrow | Specified PT |
| Cardiac Arrhythmias | Broad/Narrow | Specified PT |
| Cardiac Failure | Broad/Narrow | Specified PT |
| Cardiomyopathy | Broad/Narrow | Specified PT |
| Central Nervous System Vascular Disorders | Broad/Narrow | Specified PT |
| Convulsions | Broad/Narrow | Specified PT |
| Demyelination | Broad/Narrow | Specified PT |
| Embolic and Thrombotic Events | Broad/Narrow | Specified PT |
| Guillain-Barré Syndrome | Broad/Narrow | Specified PT |
| Hearing and Vestibular Disorders | Broad/Narrow | Specified PT |
| Hematopoietic Cytopenia | Broad/Narrow | Specified PT |
| Hypersensitivity | Broad/Narrow | Specified PT |
| Immune-mediated/Autoimmune Disorders | Broad/Narrow | Specified PT |
| Ischemic Heart Disease | Broad/Narrow | Specified PT |
| Noninfectious Myocarditis/Pericarditis | Broad/Narrow | Specified PT |
| Peripheral Neuropathy | Broad/Narrow | Specified PT |
| Thrombophlebitis | Broad/Narrow | Specified PT |
| Vasculitis | Broad/Narrow | Specified PT |

**Table 8: Algorithmic Approach for Anaphylactic Reaction**

The following criteria will be used to determine anaphylactic reaction:

- A term from Category A
- A term from Category B (Upper Airway/Respiratory) and a term from Category C (Angioedema/Urticaria/Pruritus/Flush) that occurred within 24 hours of each other.
- A term from Category D (Cardiovascular/Hypotension) and at least one of the following:
    - A term from Category B (Upper Airway/Respiratory) that occurred within 24 hours of each other.
    - A term from Category C (Angioedema/Urticaria/Pruritus/Flush) that occurred within 24 hours of each other.

| Anaphylactic Reaction | | |
|---|---|---|
| **Category** | **Scope** | **PT Search Term** |
| A | Narrow | Anaphylactic reaction |
| A | Narrow | Anaphylactic shock |

| Anaphylactic Reaction | | |
|---|---|---|
| **Category** | **Scope** | **PT Search Term** |
| A | Narrow | Anaphylactic transfusion reaction |
| A | Narrow | Anaphylactoid reaction |
| A | Narrow | Anaphylactoid shock |
| A | Narrow | Circulatory collapse |
| A | Narrow | Dialysis membrane reaction |
| A | Narrow | Kounis syndrome |
| A | Narrow | Procedural shock |
| A | Narrow | Shock |
| A | Narrow | Shock symptom |
| A | Narrow | Type I hypersensitivity |
| B | Broad | Asthma |
| B | Broad | Bronchial oedema |
| B | Broad | Bronchospasm |
| B | Broad | Cardio-respiratory distress |
| B | Broad | Chest discomfort |
| B | Broad | Choking |
| B | Broad | Choking sensation |
| B | Broad | Circumoral oedema |
| B | Broad | Cough |
| B | Broad | Cough variant asthma |
| B | Broad | Cyanosis |
| B | Broad | Dyspnoea |
| B | Broad | Hyperventilation |
| B | Broad | Irregular breathing |
| B | Broad | Laryngeal dyspnoea |
| B | Broad | Laryngeal oedema |
| B | Broad | Laryngospasm |
| B | Broad | Laryngotracheal oedema |
| B | Broad | Mouth swelling |
| B | Broad | Nasal obstruction |
| B | Broad | Oedema mouth |
| B | Broad | Oropharyngeal oedema |
| B | Broad | Oropharyngeal spasm |
| B | Broad | Oropharyngeal swelling |
| B | Broad | Pharyngeal oedema |
| B | Broad | Pharyngeal swelling |
| B | Broad | Respiratory arrest |
| B | Broad | Respiratory distress |
| B | Broad | Respiratory failure |
| B | Broad | Reversible airways obstruction |
| B | Broad | Sensation of foreign body |
| B | Broad | Sneezing |
| B | Broad | Stridor |
| B | Broad | Swollen tongue |
| B | Broad | Tachypnoea |
| B | Broad | Throat tightness |
| B | Broad | Tongue oedema |
| B | Broad | Tracheal obstruction |
| B | Broad | Tracheal oedema |
| B | Broad | Upper airway obstruction |
| B | Broad | Vaccine associated enhanced respiratory disease |

| Anaphylactic Reaction | | |
|---|---|---|
| **Category** | **Scope** | **PT Search Term** |
| B | Broad | Wheezing |
| C | Broad | Allergic oedema |
| C | Broad | Angioedema |
| C | Broad | Circumoral swelling |
| C | Broad | Erythema |
| C | Broad | Eye oedema |
| C | Broad | Eye pruritus |
| C | Broad | Eye swelling |
| C | Broad | Eyelid oedema |
| C | Broad | Face oedema |
| C | Broad | Flushing |
| C | Broad | Injection site urticaria |
| C | Broad | Lip oedema |
| C | Broad | Lip swelling |
| C | Broad | Nodular rash |
| C | Broad | Ocular hyperaemia |
| C | Broad | Oedema |
| C | Broad | Oedema blister |
| C | Broad | Periorbital oedema |
| C | Broad | Periorbital swelling |
| C | Broad | Pruritus |
| C | Broad | Pruritus allergic |
| C | Broad | Rash |
| C | Broad | Rash erythematous |
| C | Broad | Rash pruritic |
| C | Broad | Skin swelling |
| C | Broad | Swelling |
| C | Broad | Swelling face |
| C | Broad | Swelling of eyelid |
| C | Broad | Urticaria |
| C | Broad | Urticaria papular |
| D | Broad | Blood pressure decreased |
| D | Broad | Blood pressure diastolic decreased |
| D | Broad | Blood pressure systolic decreased |
| D | Broad | Cardiac arrest |
| D | Broad | Cardio-respiratory arrest |
| D | Broad | Cardiovascular insufficiency |
| D | Broad | Diastolic hypotension |
| D | Broad | Hypotension |
| D | Broad | Hypotensive crisis |
| D | Broad | Post procedural hypotension |

## 9.9. Appendix I Medical Conditions or Adverse Events by SOC/HLGT/PT

**Table 9: Medical Conditions or Adverse Events to be Presented by SOC/HLGT/PT**

| SOC | HLGT |
|---|---|
| Cardiac Disorders | Cardiac arrhythmias |
| | Cardiac disorders, signs and symptoms, NEC |
| | Cardiac neoplasms |
| | Cardiac valve disorders |
| | Coronary artery disorders |
| | Endocardial disorders |
| | Heart failures |
| | Myocardial disorders |
| | Pericardial disorders |
| Nervous System Disorders | Peripheral neuropathies |
| | PT: Guillain-Barré Syndrome * |
| | Demyelinating disorders |
| | PT: Acute disseminated encephalomyelitis * |
| | Seizures (incl subtypes) |
| Nervous System Disorders | Central nervous system infections and inflammations |
| Immune System Disorders | Allergic conditions |
| | PT: Anaphylactic reaction * |

*Only the PT under the HLGT will be presented.